Chiral Aziridination of α,β-Unsaturated Esters and Ketones using *N*-Nitrenes in the Presence of Trifluoroacetic Acid

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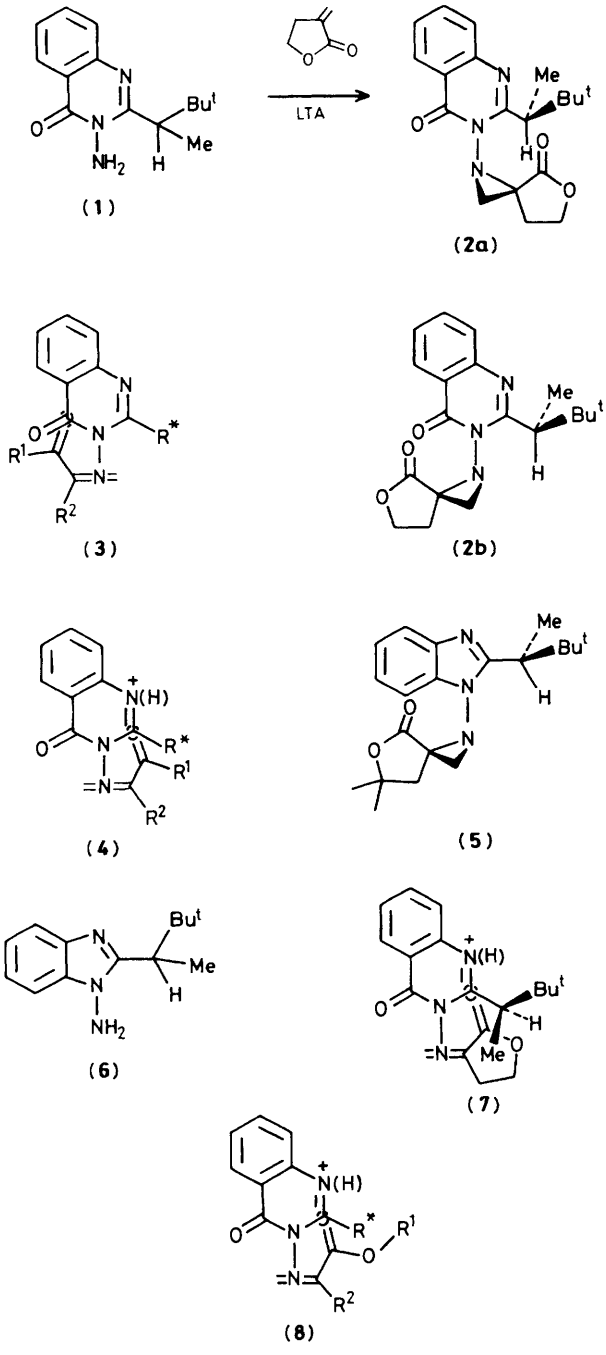
Room temperature oxidations of the *N*-aminoquinazolone (**1**) in dichloromethane containing trifluoroacetic acid (TFA) in the presence of α,β-unsaturated esters or ketones gave aziridines with modest to high stereoselectivities; the presence of TFA allows these oxidations to be carried out at −60 °C with the expected improvement in selectivity and in the presence of *ca.* 1 mol. equiv. of alkene.

Oxidation of the *N*-aminoquinazolone (**1**) in the presence of α-methylene-γ-butyrolactone was reported to give a mixture of crystalline and oily stereoisomeric aziridines (**2**) with very little asymmetric induction (ratio crystalline : oily 1 : 1.3).[1] In the presence of small amounts of trifluoroacetic acid (TFA) (3.4 mol. equiv.), however, the reaction was stereospecific and only the crystalline stereoisomer was formed. This effect of TFA was ascribed to a change in transition state geometry

Table 1. Ratios of aziridine stereoisomers from oxidation of *N*-aminoquinazolone (**1**) by LTA in the presence of various α,β-unsaturated esters and ketones (4 mol. equiv.) at room temperature with and without TFA (3.4 mol. equiv.).

Entry	Alkene	Stereoisomer ratio without TFA	Stereoisomer ratio with TFA	Yield/%[a]
1	$H_2C{=}CHCO_2Me$	2.4 : 1	1 : 8.7	50(77)
2	$H_2C{=}CHCO_2Me$	—	1 : 23[b]	65(72)
3	$H_2C{=}CHCO_2Bu^t$	2.1 : 1	14 : 1[c]	39(75)[d]
4	$H_2C{=}C(Me)CO_2Me$	1.2 : 1	1 : 5.2[c]	46(72)[d]
5	*trans*-$MeCH{=}CHCO_2Me$	—	7.0 : 1[c]	58(78)
6	$H_2C{=}CHC(O)Me$	1.25 : 1	1 : 6.5	62(78)
7	*trans*-$H(Me)C{=}CHC(O)Me$	1.2 : 1	8.6 : 1[c]	52(82)

[a] Isolated yield of the major stereoisomer in the TFA oxidation after separation by chromatography (^{1}H n.m.r. yield of major stereoisomer in brackets). The major difference in n.m.r. and isolated yields is the result of neglecting mixed fractions in the chromatography. [b] Oxidation carried out at −60 °C in the presence of 1.1 mol. equiv. of alkene and 10 mol. equiv. of TFA without separation of stereoisomers. [c] Major stereoisomer crystalline. [d] Major stereoisomer in TFA oxidation separated by crystallisation but yield is not optimised.



All compounds are racemic.

from (3) to (4) brought about by protonation at N-1 of the *N*-aminoquinazolone and hence the derived *N*-nitrene.

Oxidation of the *N*-aminoquinazolone (1) in the presence of a number of α,β-unsaturated esters and ketones with lead tetra-acetate (LTA) in the presence of TFA[2] has been found to lead to reasonable yields of aziridines and significant asymmetric induction (Table 1). We find that the use of TFA in these oxidations has two advantages: (i) the reaction can be carried out at −60 °C with the expected improvement in the degree of induction; and (b) the alkene may be employed in approximately equimolar quantities with only small losses in yield. The results in Table 1 (except entry 2) were obtained at room temperature in the presence of 4 mol. equiv. of the alkene. Entry 2 is the reaction at −60 °C using only 1.1 mol. equiv. of methyl acrylate. From a comparison of entries 1 and 2 it is clear that an increase in selectivity occurs at −60 °C with little loss in yield. From a number of experiments carried out using 1.1 mol. equiv. of the alkene, it appears that TFA stabilises the protonated N-1 nitrene against intramolecular decay and also that the N-1 protonated aminoquinazolone (1) is less reactive at its free amino group towards the N-1 protonated nitrene.

Entries 1 and 3 in Table 1 strongly suggest that the derived aziridines from methyl and t-butyl acrylate have the opposite induced configuration at the newly-created chiral centre. This conclusion follows from a comparison of the stereoisomer ratios in the absence and presence of TFA. In the absence of TFA, the transition state in both cases will resemble (3) and low but similar degrees of induction are anticipated which is found to be the case. In the presence of TFA, the predominant stereoisomer resulting from addition to methyl acrylate is the minor one produced in the absence of TFA whereas the reverse is obtained in addition to t-butyl acrylate.

The relative configuration of the two chiral centres in the crystalline stereoisomer of (2) was predicted[1] to be (2b) by analogy with that of the single stereoisomer (5) obtained from oxidation of the corresponding *N*-aminobenzimidazole (6) in the presence of α-methylene-γ,γ-dimethyl-γ-butyrolactone (in the absence of TFA) whose structure was confirmed by *X*-ray crystallography.[3] An *X*-ray crystal structure determination of this stereoisomer, however, shows it to have the structure (2a).[4] We suggest that this unexpected change in the induced configuration at the spiro-centre is evidence for protonation of the *N*-nitrene at the N-1 position. The transition state for the addition, therefore, must resemble (7) in which methyl and hydrogen have exchanged their site occupancy [by comparison with the corresponding transition state leading to (5)] possibly because of preferential solvation of N-1 on the side of the quinazolone ring opposite to the t-butyl group.†

Additions of the *N*-nitrene derived from (1) to the α,β-unsaturated esters in Table 1 are accommodated by a transition state (8) resembling (7) but with the esters present in their preferred conformations.[5] For a given configuration of (*R**), the face of the alkene preferentially attacked will depend on the nature of both R^1 and R^2 in a predictable way.

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† The change in the transition state geometry from (3) → (4) in the presence of TFA could be interpreted as resulting from protonation at the quinazolone carbonyl oxygen but it is difficult to account for the difference in induced configuration in (2a) by comparison with (5) if this were the case.